

Amendments to the Claims

(Marked up version)

Please amend the following claims by deleting the words in brackets and inserting the underlined words.

Please cancel Claims 1-10.

11. (Once Amended) A composition for inhibiting endothelial cell proliferation comprising tissue factor pathway inhibitor in a pharmaceutically acceptable carrier.

12. (Once Amended) The composition of Claim 11, wherein the tissue factor pathway inhibitor comprises an active fragment of the Kunitz-3 domain of tissue factor pathway inhibitor, wherein the active fragment inhibits cell proliferation.

13. (Cancel) The composition of Claim 12 wherein the active fragment inhibits endothelial cell proliferation.

14. The composition of Claim 12 wherein the active fragment inhibits angiogenesis.

15. The composition of Claim 12 wherein the active fragment inhibits angiogenesis-related disease.

16. The composition of Claim 15, wherein the angiogenic-related disease is a disease selected from the group consisting of cancer, arthritis, macular degeneration, and diabetic retinopathy.

17. The composition of Claim 12 wherein the active fragment is a peptide having an amino acid sequence within the amino acid sequence set forth in SEQ ID NO. 1.

19. (Cancel) The composition of Claim 11 wherein the active fragment contains the Kunitz-3 domain or a fragment thereof

20. (Once Amended) The composition of Claim [10] 11, wherein the carrier is a sustained-release matrix.

Amendments to the Specification
(Marked Up Version)

Please amend Page 1 of the specification by inserting the underlined words immediately following the title, "Compositions and Methods for Inhibiting Cellular Proliferation" and preceding the paragraph entitled "Field of Invention":

CROSS-REFERENCE TO RELATED PATENT APPLICATIONS

The present application is a continuation application United States Patent Application Serial No. 09/227,955 filed January 11, 1999 (now abandoned), which is a continuation application of United States Patent Application Serial No. 08/796,850 filed February 6, 1997 which issued as United States Patent No. 5,981,471 on November 9, 1999.

REMARKS

The present application is directed to methods for the inhibition of cellular proliferation by the administration of Tissue Factor Pathway Inhibitor (TFPI). TFPI homologs, or active fragments thereof. The TFPI, TFPI homologs, or active fragments thereof, are combined with a pharmaceutically acceptable excipient and are useful for treating diseases associated with undesirable cell proliferation including angiogenesis and angiogenesis-related diseases.

Claims 11-17 and 19-20 are currently pending in the above-identified application. In response to the Office Action dated October 9, 2002 and in order to facilitate prosecution, Claims 11, 12, and 20 are herein amended, and Claims 1-10, 13 and 19 have been cancelled. No new matter has been added and support for the claims is found in the specification. Applicants submit the following remarks in an effort to address the rejections raised in the Office Action.

Status of Claims

In the October 9, 2003 Claim 20 was considered to be withdrawn because it was dependent on Claim 10 (belonging to the non-elected group). Applicants have however amended Claim 20 so that it now depends on Claim 11 (belonging to the elected group).

Priority

In the Office Action dated October 9, 2003, the Examiner rejected the claim for priority under 35 U.S.C. §120 because it was not in the first sentence of the specification. Applicants have herein requested amendment of the specification and accordingly withdrawal of this rejection is requested.

Claim Rejections 35 U.S.C. §112, first paragraph

In the Office Action dated October 9, 2003, the Examiner stated that Claims 12-17 are rejected under 35 U.S.C. §112, first paragraph because the specification while being enabled for "active" fragments comprising Kunitz-3 domain, does not reasonably provide enablement for any randomly taken fragments of TFPI.

Claim Rejections 35 U.S.C. §102 and 103

In the Office Action dated October 9, 2003, the Examiner stated that Claims 11-17 and 19 are rejected under 35 U.S.C. §102(a) as being anticipated under Steinhubl *et al.* (*J. Amer. College of Cardiology* 29 (2), 243A, 1997) or Khouri *et al.* (*Surgical Forum* 46, 389-391, 1995) or Markland *et al.* (United States Patent No. 5,795,865).

The Examiner stated that Steinhubl *et al.* and Khouri *et al.* teach the inhibition of neointimal proliferation and therefore anticipate applicants' claims. Applicants have herein amended the claims so that they are now specifically directed to inhibition of endothelial cell proliferation. As explained below, one skilled in the art would not expect compositions that inhibit neointimal proliferation to also inhibit endothelial cell proliferation and accordingly the teachings of Steinhubl *et al.* and Khouri *et al.* do not anticipate the present invention.

In contrast to applicants' claimed compositions, which are directed to the inhibition of endothelial cell proliferation, Khouri *et al.* disclose methods and compositions directed at the prevention of thrombus formation associated with neointimal hyperplasia. Khouri *et al.* specifically teach that irrigation with TFPI inhibits intimal hyperplasia by irreversibly binding to vessel walls, inducing formation of a pacifying scab, and preventing platelet aggregation and thrombus formation (Khouri *et al.* p. 390). A thrombus, an accumulation of platelets and the formation of fibrin, is unrelated to endothelial cell proliferation, and consequently Khouri *et al.* do not teach the use of TFPI for purposes of modifying or inhibiting endothelial cell proliferation. Whereas thrombus formation is the random aggregation of cellular matter, the proliferation of endothelial cells is an organized, molecular event, typically resulting in the development of new blood vessels. Accordingly, the use of TFPI by Khouri *et al.* for the prevention of aggregation of cellular matter fails to anticipate applicants' use of TFPI for inhibition of endothelial cell proliferation.

The abstract of Steinhubl *et al.* describes experiments in which TFPI was administered to inhibit neointimal hyperplasia. Steinhubl *et al.* measured the neointimal area after over-expansion balloon injury followed by treatment with TFPI, heparin, or the combination of TFPI and heparin. Applicants respectfully assert that the teachings of Steinhubl *et al.* are directed only

(1994) as the "abnormal migration and proliferation of vascular smooth muscle cells with the associated deposition of extracellular connective tissue matrix" (Davies *et al.* abstract).

Neointimal hyperplasia is part of the complex healing process following vascular injury and is generally not associated with neovascularization. Arterial or vein damage is normally followed by platelet aggregation and thrombus formation at the site of the injury, an acute inflammatory response, proliferation of vascular smooth muscle cells, and extracellular matrix deposition (Faxon *et al.* *Prog Cardiovasc. Dis.* 40(2):129-40 (1997)). Since TFPI is known to inhibit fibrin generation and thus, thrombus formation (one of the first steps of the physiological response to vascular injury), measurement of the neointimal area by Steinhubl *et al.* after treatment with TFPI does not necessarily indicate inhibition of undesirable smooth muscle cell proliferation. However, even if one skilled in the art concludes that Steinhubl *et al.* does teach that TFPI has an affect on replication of smooth muscle cells, smooth muscle cells are distinctively different from endothelial cells. Endothelial cells constitute the innermost layer of all blood vessels. Smooth muscle cells compose a portion of the protective, thick wall that covers only large vessels such as arteries and veins. (Albert *et al.*, *MOLECULAR BIOLOGY OF THE CELL*, Garland Publishing, Inc., New York, (1982), pages 906-908). Thus, while the basic role of endothelial cells is to provide a smooth surface that enables blood cells and platelets to flow without being damaged, smooth muscle cells play a functional role in affecting blood vessel diameter. Given the significant physiological and functional differences between the smooth muscle cells and endothelial cells, it is unlikely that one skilled in the art would be motivated to use TFPI for inhibition of endothelial cells based on teachings in the prior art concerned with the use of TFPI for prevention of neointimal hyperplasia. Finally, neointimal hyperplasia and neovascularization are two distinctively different physiological processes: inhibition of endothelial cell proliferation has not been associated with inhibition of neointimal hyperplasia, and inhibition of smooth muscle cells has not been shown to prevent formation of blood capillaries.

Unlike applicants' method, which is direct to the administration of TFPI for the inhibition of endothelial cell proliferation, Khouri *et al.* and Steinhubl *et al.* are directed to the use of TFPI for the inhibition of intimal hyperplasia, specifically prevention of thrombus formation and

therefore, that neither Khouri *et al.*, nor Steinhubl *et al.* anticipate applicants' compositions and request that the Examiner withdraw this rejection.

In the Office Action dated October 9, 2003, the Examiner further stated that Claims 11-17 and 19 are rendered obvious under 35 U.S.C. §103(a) over Markland *et al.* (United States Patent No. 5,795,865).

The Examiner noted that the peptide of SEQ ID NO: 35 in Markland *et al.* is a preferred inhibitor of kallikrein and that this peptide reads on compositions comprising TFPI fragments, fragments of Kunitz-3 domain in particular. Applicants respectfully note that Markland *et al.* is unrelated to inhibition of endothelial cell proliferation, as it claims methods directed to treating disorders attributable to excessive kallikrein activity. As evidenced by the teachings of Schutte *et al.* (Kininogenesis: Kallikrein, Symp. Physiol. Prop. Pharmacol. Ration., 4th, 161-177, Eds: Haberland, G. *et al.* Schattauer, Stuttgart, 1977), activity of kallikreins cannot be confined to any particular physiological process. Accordingly, one skilled in the art would not expect inhibition of kallikrein activity to be influential for any specific physiological process without extensive experimentation based on Markland *et al.*

Not only are the general effects of excessive kallikreins on a particular class of cells unpredictable, the effects of kallikreins at various stages of cellular development are also unpredictable:

"The mitogenic effects of Kallikrein, then, are by no means uniform but, viewed on the whole, dependent on dosage, duration, mode and route of administration and also on the localization, type and baseline status of the cell population in question. This is what our studies and those of other research teams have shown. These findings need to be verified by more extensive studies."
(Schutte *et al.* p. 162)

In conclusion therefore, although Markland *et al.* teach inhibition of disorders caused by excessive kallikreins by administering proteins comprising Kunitz domain-containing proteins and peptides, Markland *et al.* fail to provide any teaching of administering such proteins for inhibiting endothelial cell proliferation.

presently claimed invention. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Conclusion

In light of the amendments, Applicants are of the opinion that Claims 11-17, 19 and 20 are now in condition for allowance. Such action is respectfully requested. If the Examiner believes any informalities remain in the application which may be corrected by Examiner's Amendment, or there are any other issues which can be resolved by telephone interview, a telephone call to the undersigned attorney at (404) 745-2463 is respectfully solicited.

Respectfully submitted,



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Claims Pending Following Entry of this Amendment

11. A composition for inhibiting endothelial cell proliferation comprising tissue factor pathway inhibitor in a pharmaceutically acceptable carrier.

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